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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/027,201 | 12/20/2001 | Stephen Quirk | 1443.027US1 | 1416 |

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| EXAMINER | |
|---|---|
| COUNTS, GARY W | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 01/24/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/027,201 | QUIRK, STEPHEN | |
| | Examiner | Art Unit | |
| | Gary W. Counts | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7,9-18 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7,9-18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Status of the claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/11/06 has been entered.

### *Election/Restrictions*

Applicant states that the subject matter of claim 23 is properly part of the present invention because, for example, claim 1 is generic to claim 23 and therefore, Applicant requests reconsideration of claim 23. This is not found persuasive because claim 1 is not generic to claim 23. As stated in the previous office action Claim 23 requires a mixture of aspartic acid, glutamic acid, asparagines, arginine, and serine amino acids and claims 1-22 do not require this limitation. Further, claim 1 specifically requires that the label is covalently linked to the proteinoid microsphere and claim 23 does not require this limitation. Therefore, the restriction requirement is maintained.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 the recitation "the signal amplification" there is insufficient antecedent basis for this limitation. Further, it is unclear what applicant intends by claim 16, what signal? Is applicant comparing the proteinoid microsphere with the label and immobilized binding agent to that of a labeled antibody that does not comprise a proteinoid? Please clarify.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1, 2, 5, 7, 9, 12-18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohrmann et al (US 6,193,953) in view of Steiner et al (US 4,925,673) and Kayyem et al (US 6,232,295).

Lohrmann et al disclose protein microparticles that can be comprised of chemically synthesized amino acid polymers (col 5, lines 40-57). Lohrmann et al disclose that the microparticles can comprise fluorines or $I^{125}$ (radioisotope)(label) (col 15, lines 1-16). Lohrmann et al also disclose that the microparticles can comprise a targeting moiety such as an antibody linked to the microparticle (col 13, lines 27-29). Lohrmann et al disclose that the microparticles can be used in imaging applications such as MRI (col 15, lines 5-12).

Lohrmann et al differ from the instant invention in failing to specifically state that their protein microparticle is a proteinoid microparticle. Lohrmann et al also differ from the instant invention in failing to teach the label covalently linked to the proteinoid microsphere.

Steiner et al discloses proteinoid microspheres (microparticles). Steiner et al discloses that the proteinoid microspheres are man made condensation polymers produced by random or directed assembly of natural or synthetic amino acids. Steiner et al disclose methods of producing the microspheres by using heat to condense the amino acids (see examples). Steiner et al disclose a mixture of amino acids comprising an acidic amino acid and a basic amino acid (col 5, lines 27-51). Steiner also teaches that these condensed polymers provide for protein microparticles which are non-toxic and can be very finely tuned for solubility characteristics (col 3) .

Kayyem et al disclose polymeric delivery vehicles that are tissue specific used in MRI applications. Kayyem et al disclose that a contrasting agent (label) is attached (linked) to the polymeric delivery vehicle. Kayyem et al disclose that the label is covalently attached to the polymeric delivery vehicle. Kayyem et al teaches that gadolinium and fluorine are interchangeable as labels in imaging (col 4). Kayyem et al disclose that this provides for a safe and effective means and for improved targeted delivery of contrast agents to specific cells or tissue (col 2-col 4) and allow for medical imaging.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the protein microparticles of Lohrmann et al using condensed amino acids such as taught by Steiner et al because Lohrmann et al specifically teaches that the protein microparticles can be comprised of synthesized amino acid polymers and Steiner et al specifically teaches that proteinoid micropsheres are man made condensation polymers produced by random or directed assembly of synthetic amino acids and that these provides for protein microparticles which are non-toxic and can be very finely tuned for solubility characteristics (col 3) . Therefore, one of ordinary skill in the art would have a reasonable expectation of success to form the protein microspheres of Lohrmann et al by condensing amino acids such as taught by Steiner et al. Therefore, the combination of Lohrmann et al and Steiner et al disclose proteinoid microspheres.

It also would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently attach labels to the polymeric surface such as taught

by Kayyem et al on the modified protein microparticles of Lohrmann et al because Lohrmann et al specifically disclose that their microparticles can be polymeric (col 5) and used in imaging applications (col 15, lines 5-12) and also comprises labels such as fluorine and further because Kayyem et al teaches that this provides for a safe and effective means and for improved targeted delivery of contrast agents to specific cells or tissue (col 2-col 4) and allow for medical imaging. Therefore, one of ordinary skill in the art would have a reasonable expectation to attach labels as taught by Kayyem et al on the modified proteinoid microparticle of Lohrmann et al.

With respect to the recitation "and the proteinoid microsphere is stable in solution". Since the combination of the above references teach the same microspheres as recited. The modified microspheres of Lohrmann et al would be stable in solution.

With respect to claims 5 and 13-16 as recited in the instant claims. The claims are directed to intended use of the proteinoid microspheres and therefore are not given patentable weight. Further, since the combination of references disclose the claimed invention and the Applicant has not recited any structural differences over the prior art, the prior art is capable of performing the intended use.

7. Claims 3, 4, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohrmann et al in view of Steiner et al and Kayyem et al and further in view of Mathiowitz et al (US 5,271,961).

See above for the teachings of Lohrmann et al, Steiner et al and Kayyem et al.

Lohrmann et al., Steiner et al., and Kayyem et al differ from the instant invention in failing to teach the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a cross linking agent.

Mathiowitz et al disclose protein microspheres that can be modified. Mathiowitz et al disclose that the modification of the protein can be done by cross-linking the protein using agents such as glutataldehyde (col 6, lines 51-62). Mathiowitz et al disclose that such modifications provides a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases (col 5, lines 50-56).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate cross-linking as taught by Mathiowitz et al into the modified microspheres of Lohrmann et al because Mathiowitz et al shows that such modifications provides a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases.

***Response to Arguments***

8. Applicant's arguments filed 11/08/06 have been fully considered but they are not persuasive.

NOTE: Independent claim 9 was not amended to include the limitation "an external surface". Therefore, all previous rejections are maintained for the previous reasons and applicant's arguments directed toward covalent attachment to an external surface do not apply to claim 9.

Applicant argues that Steiner is the only reference that mentions proteinoid microspheres and that Steiner is limited to encapsulated pharmacological agents and teaches away from externally attaching agents to the surface of microspheres. This is not found persuasive because (1) it appears that applicant is arguing the references individually and in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and (2) although Steiner, which is used as a secondary reference is the only reference which explicitly states proteinoid microspheres, the Lohrmann (primary) reference clearly teaches the microparticle is a protein microparticle and clearly teaches the microparticle is comprised of amino acid polymers (col 5) and also teaches that the microparticles are heat treated (thermal) (col 16, example 4). Therefore, the microparticles of Lohrmann et al are protein microparticles that have been heat treated and comprise the same materials (amino acids) as recited. Examiner has relied on Steiner et al for the term proteinoid microparticle and condensing of amino acids, and since Lohrmann et al specifically teaches that their protein microparticles can be chemically synthesized amino acids and Steiner et al specifically teaches that proteinoid micropsheres are man made condensation polymers produced by random or directed assembly of synthetic amino acids and that these provides for protein microparticles which are non-toxic and can be very finely tuned for solubility

characteristics (col 3) . Therefore, one would be motivated to combine the teachings of Lohrmann et al and Steiner et al and would have a reasonable expectation of success.

Applicant argues that Lohrmann is limited to ultrasound contrast microparticles made of a protein shell and encapsulated air or gas. This is not found persuasive because Lohrmann is not limited to ultrasound contrast microparticles. Lohrmann et al clearly teaches (col 15) that the microparticles can be used in MRI and can comprise fluorine or $I^{125}$ (radioisotope) labels. Also, Examiner has not relied upon Lohrmann et al for teaching the fluorine bound to the surface but rather has relied upon Kayyem et al for teaching that it is known in the art to covalently bind fluorine and gadolinium to polymeric carrier vehicles. Applicant further argues that Steiner discourages from combining Steiner with Lohrmann. Applicant directs examiner attention to col 3, lines 27-29 of Steiner. This is not found persuasive because the disclosure in Steiner "proteinoids are far more resistant that proteins to cleavage by digestive enzymes" is directed to embodiments in which the proteinoid is in the digestive tract, and Examiner has not relied upon Steiner for the use of the microparticles but rather as relied upon Steiner for teaching the formation of a protein microsphere.

Applicant further argues that neither Steiner nor Lohrmann disclose the labels contemplated by the present invention. In particular, the terms "fluorophore", "chemiluminescent", "radioisotope" and "paramagnetic". This is not found persuasive because as stated in the previous office action and as stated above Lohrmann et al teaches the use of fluorine and $I^{125}$ which are known in the art to be "radioisotopes.

Applicant argues that Steiner would discourage the skilled artisan from using proteins rather than proteinoid microspheres. This is not found persuasive because applicant is once again arguing the references individually and further because as stated above the disclosure in Steiner "proteinoids are far more resistant that proteins to cleavage by digestive enzymes" is directed to embodiments in which the proteinoid is in the digestive tract, and Examiner has not relied upon Steiner for the use of the microparticles but rather as relied upon Steiner for teaching the formation of a protein microsphere.

Applicant argues that the terms microsphere and microcapsule appear nowhere in the Kayyem disclosure, thereby further indicating that the teachings of Kayyem are not relevant to those of Steiner and/or Lohrmann. This is not found persuasive because although Kayyem does not specifically recite microspheres or microcapsules, Kayyem et al is considered analogous art because Kayyem et al teaches polymeric delivery vehicles which are directed to a specific target and are used with contrast agents in imaging (such as MRI) (all of which are taught by Lohrmann).

Applicant argues that Mathiowitz is limited to incorporation of agents into micorspheres rather than covalently attaching agents to the external surface of the microsphere. This is not found persuasive because Examiner has not relied upon Mathiowitz for this teaching but rather has relied upon the combination of Lohrmann et al., Steiner et al and Kayyem et al for this limitation. Applicant argues that Mathiowitz is limited to methods for making protein microspheres by solvent evaporation of a solution of proteins (not amino acids). This is not found persuasive because Mathiowitz et al

clearly teaches that the protein can by modified by crosslinking amino acids (col 6, lines 54-62). Further, proteinoids are thermal protein polymers containing amino acids and proteins are polymers of amino acids (5,679,377, col. 1, lines 25-50). Applicant further argues that Mathiowitz emphasizes that the protein microspheres are made under gentle conditions and teaches that the proteins are treated with crosslinking agent prior to formation of protein microspheres. This is not found persuasive because the current claims are not directed to methods of making but rather are directed to the proteinoid microspheres thus the argument is not on point. Applicant further states that mere mention of a cross-linker reference does not mean that one of skill in the art would necessarily know how or why to use the cross-linking agent and that there must be some teaching in the cited references to motivate one of skill in the art to make and use the invention. This is not found persuasive because as stated above the art of proteinoids and protein microspheres is analogous art because, proteinoids are thermal protein polymers containing amino acids and proteins are polymers of amino acids and Mathiowitz et al specifically teaches that cross-linking provides for a protein having enhanced or altered thermal stability and surface reactivity thus motivation is clearly provided.

Applicant's argues that there is no motivation to modify the teachings of Steiner on unstable proteinoid microspheres by addition the crosslinking agent disclosed in Mathiowitz. This is not found persuasive because the rejection is not based on the mere combination of Steiner and Mathiowitz but rather is based on the combination of Primary reference Lohrmann in view of Steiner et al and Kayyem et al and further in

view of Mathiowitz et al thus it appears that Applicant is arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art Unit 1641
January 11, 2007

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